

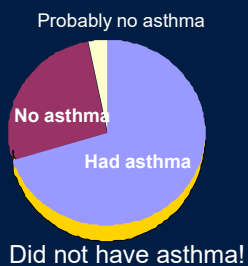
Severe Persistent Therapeutics: The New Landscape

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Disclosures

- Professor of Medicine; National Jewish Health; University of Colorado, Denver
- Astra Zeneca: Speaker, advisor
- GSK: Advisor, research
- Sanofi/Regeneron: Advisor
- “Opinions and assertions herein are not representative of either entity but are of my own opinion”

Step #1. Make sure the patient has asthma

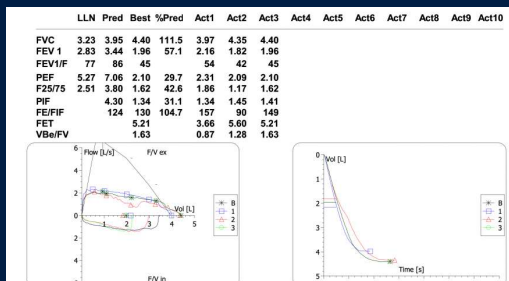


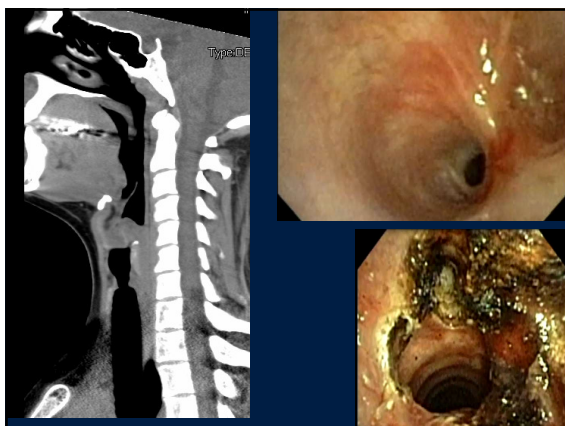
- 150 pts referred to difficult asthma clinic at NJH
 - Extensive evaluation
- Similar to results from Canada in milder asthma (random dialing approach evaluating ~500 “asthmatics” *Aaron et al, CMJ 2008*)

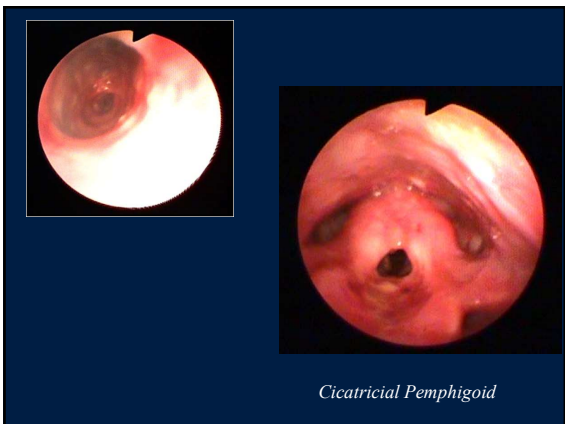
Differential Dx Of Wheezing

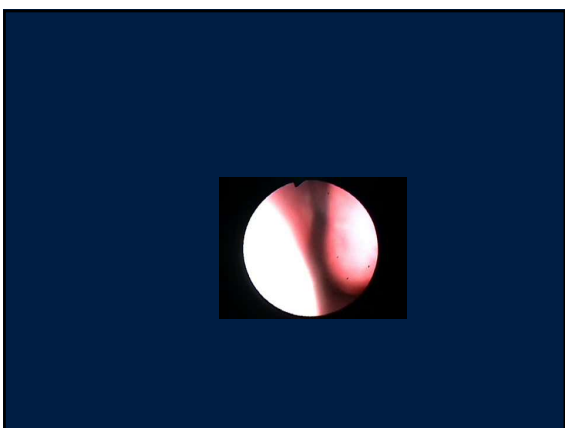
- "Asthma"
- VCD
- ABPA
- Chronic Eosinophilic Pneumonia
- Airway Tumors
- Bronchostenosis/TBM/DAC
- CHF
- Infection
- * TB
- * Tonsils
- * Foreign body
- * Goiter
- * Post polio syndrome
- * COPD
- * PE
- * Fixed lesions

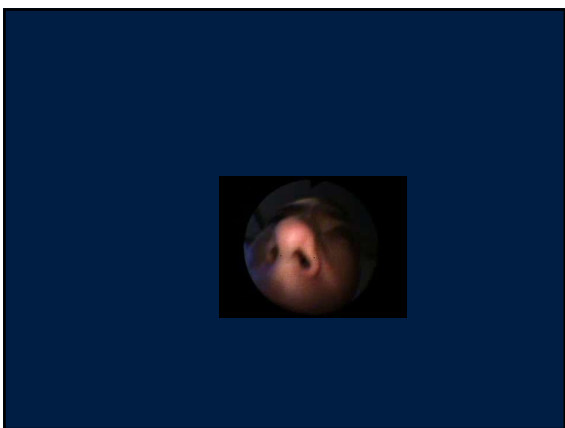
Spiro

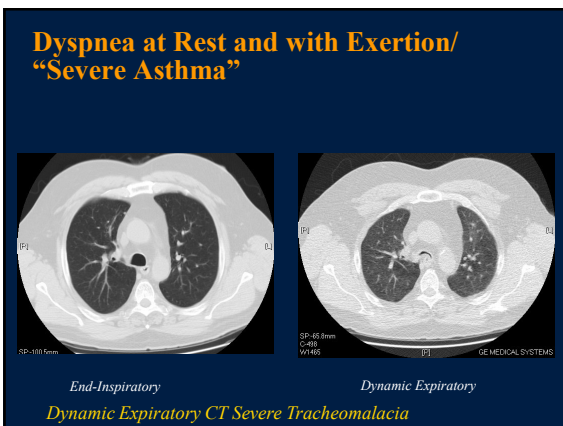


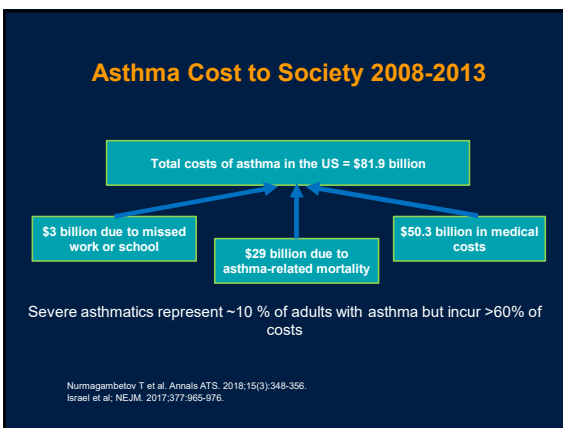


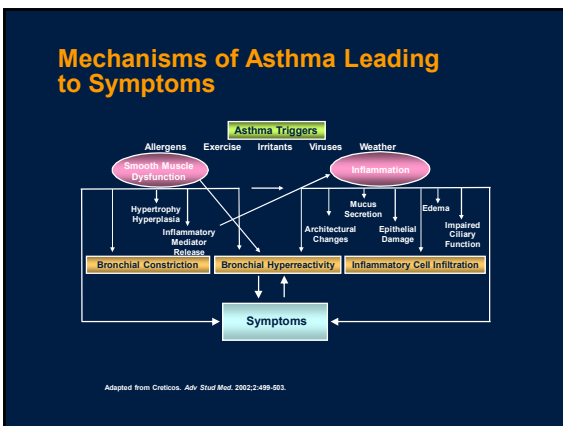




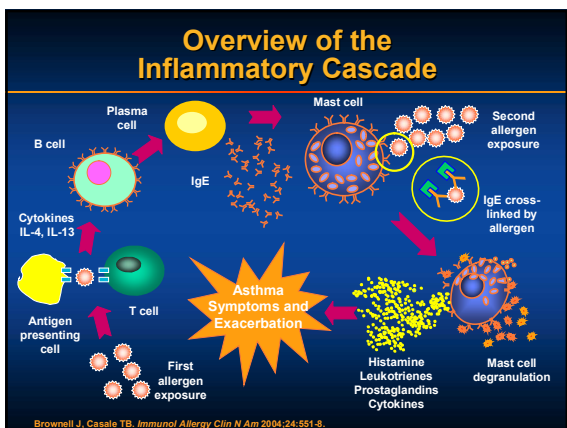


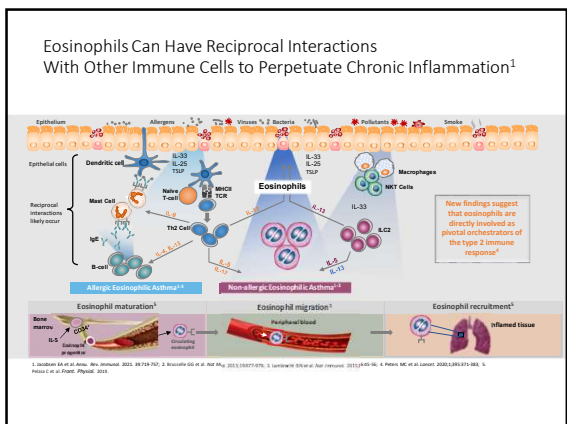


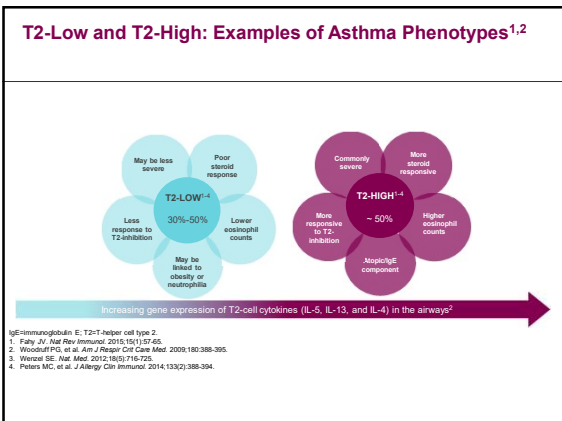


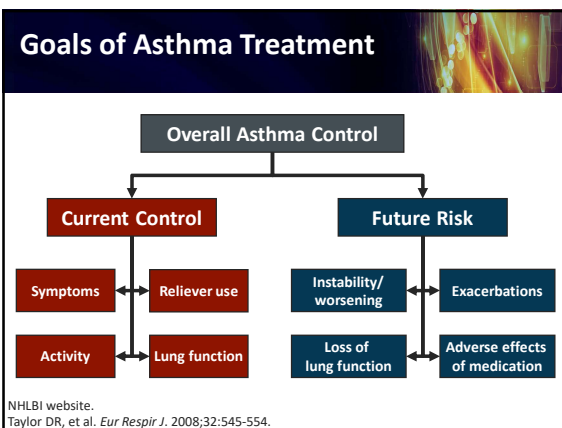













- ### Goals of Asthma Therapy
- Minimal or no chronic symptoms day or night
 - Minimal or no exacerbations
 - No limitations on activities; no school/work missed
 - Maintain (near) normal pulmonary function
 - Minimal use of inhaled short-acting beta₂-agonist
 - Minimal or no adverse effects from medications
- Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2022.
 NHL, NHLBI. May 2023 (reprint). NIH Publication No. 02-5075.

Asthma Therapy Through the Ages

G. Cardano <ul style="list-style-type: none">• Diet• Exercise• Sleep• No feathers	T. Willis <ul style="list-style-type: none">• Field gums• Musk• Vitriolic ether	J. Floyer <ul style="list-style-type: none">• Gill• Hyssop• Syrup of sulphur• Bleeding	W. Osler <ul style="list-style-type: none">• Atropine• Morphine• Chloroform• Lobelia
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1500s 1600s 1700s 1800s



- Amyl nitrate
- Asthma cigarettes


Asthma Therapy – 1800s



Asthma Therapy in the 1900s

<ul style="list-style-type: none">• Adrenaline• Methyl xanthines	<ul style="list-style-type: none">• Oral steroids• β-agonists	<ul style="list-style-type: none">• Long-acting β_2-agonists• Leukotriene modifiers
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1900-30s 1940s 1950s 1970s 1990s



- Systemic steroids (ACTH)
- Cromones
- Inhaled steroids
- β_2 -selective agonists

Biologics

Biomarkers

Summary: Increased Eosinophils in Asthma

Elevated eosinophils were correlated with:

- Increased asthma severity^{1,2}
- Worsening lung function³⁻⁵
- Increased risk of exacerbations^{6,7}
- Increased rates of hospitalizations and ED visits⁸

1. Bourque F et al. *Am J Respir Crit Care Med*. 2002;165:1022-1028. 2. Cook R et al. *Am J Respir Crit Care Med*. 2003;168:1241-1246. 3. Brodeur M et al. *Respir Med*. 2010;104:1234-1242. 4. Woodruff PG et al. *J Allergy Clin Immunol*. 2005;115:1232-1238. 5. McGrath WM et al. *Am J Respir Crit Care Med*. 2012;185:637-642. 6. Singer RS et al. *J Allergy Clin Immunol Pract*. 2014;2:761-767. 7. FitzGerald JM. *Am J Respir Crit Care Med*. 2005;171:261-267.

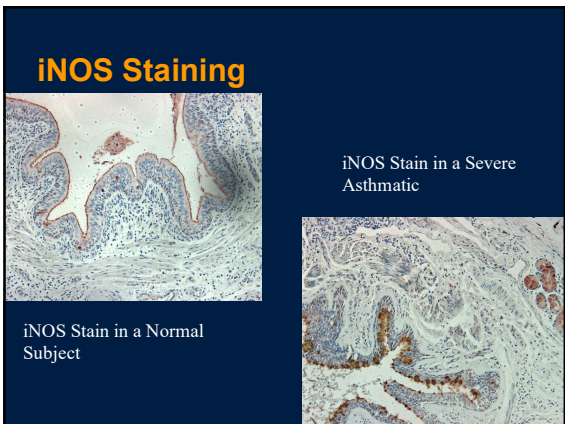
Increased Eosinophils in Asthma: Major Risk Factor for Exacerbations

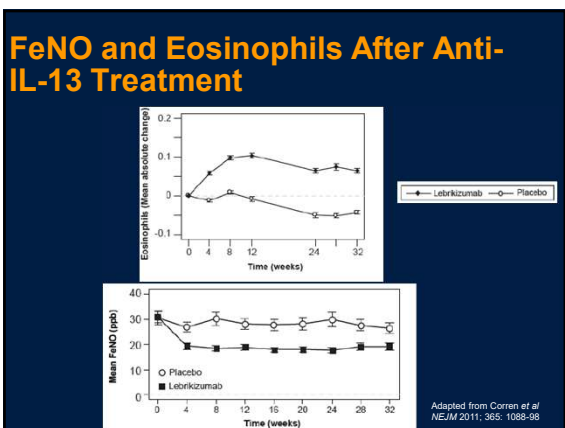
Risk Factor	Odds Ratio (95% CI)	p-value
Age (per year increase)	1.007 (1.005-1.008)	<0.001
Gender (F vs. M)	1.21 (1.14-1.28)	<0.001
Overweight vs. normal BMI	1.80 (1.71-1.90)	<0.001
Obesity vs. normal BMI	1.75 (1.61-1.91)	<0.001
Smoker vs. non-smoker	1.14 (1.06-1.22)	<0.001
Exacerbator vs. non-exacerbator	0.93 (0.88-0.99)	0.024
Blood eosinophils >400 cells/µL, F > 400 cells/µL, M > 300 cells/µL	1.49 (1.29-1.70)	<0.001
GERD	1.00 (1.04-1.10)	<0.001
Dyslexia (dys 1 or 2)	1.11 (1.05-1.17)	<0.001
Eosinophilia	1.08 (1.03-1.14)	0.003
GERD	1.12 (1.05-1.20)	<0.001
Proteinuria	1.10 (1.04-1.16)	<0.001
Asthma-specific prescription	1.23 (1.11-1.36)	<0.001

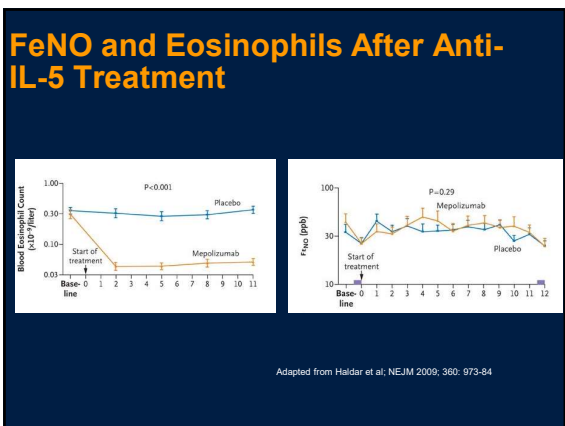
Blood eosinophil >400 cells/µL:

- Single best predictor of multiple exacerbations
- ↑ likelihood of ≥2 exacerbations by 1.5-fold

Adapted from Price D et al. *J Asthma Allergy*. 2016;9:1-12.
 BMI = body mass index; CI = confidence interval; GERD = gastroesophageal reflux disease; M = male.







Anti IL-5 Improves Outcomes in Eosinophilic Asthma

- Mepolizumab, benralizumab, reslizumab
 - Reduce Eosinophils
 - Reduce Exacerbations
 - Improve Lung Function
 - Improve Quality of Life
 - Facilitate Corticosteroid Withdrawal

Biologics can target IL4 and IL13

Inflammatory mechanisms and pathobiologic features leading to severe asthma
Inflammatory mechanisms associated with granulocytic inflammation

Type 2 inflammation (Allergic)
 IL-4, IL-5, IL-13, IL-31, IL-25, IL-33, IL-17, IL-17A, IL-17F, IL-17C, IL-17D, IL-17E, IL-17F, IL-17G, IL-17H, IL-17I, IL-17J, IL-17K, IL-17L, IL-17M, IL-17N, IL-17O, IL-17P, IL-17Q, IL-17R, IL-17S, IL-17T, IL-17U, IL-17V, IL-17W, IL-17X, IL-17Y, IL-17Z, IL-17AA, IL-17AB, IL-17AC, IL-17AD, IL-17AE, IL-17AF, IL-17AG, IL-17AH, IL-17AI, IL-17AJ, IL-17AK, IL-17AL, IL-17AM, IL-17AN, IL-17AO, IL-17AP, IL-17AQ, IL-17AR, IL-17AS, IL-17AT, IL-17AU, IL-17AV, IL-17AW, IL-17AX, IL-17AY, IL-17AZ, IL-17BA, IL-17BB, IL-17BC, IL-17BD, IL-17BE, IL-17BF, IL-17BG, IL-17BH, IL-17BI, IL-17BJ, IL-17BK, IL-17BL, IL-17BM, IL-17BN, IL-17BO, IL-17BP, IL-17BQ, IL-17BR, IL-17BS, IL-17BT, IL-17BU, IL-17BV, IL-17BW, IL-17BX, IL-17BY, IL-17BZ, IL-17CA, IL-17CB, IL-17CC, IL-17CD, IL-17CE, IL-17CF, IL-17CG, IL-17CH, IL-17CI, IL-17CJ, IL-17CK, IL-17CL, IL-17CM, IL-17CN, IL-17CO, IL-17CP, IL-17CQ, IL-17CR, IL-17CS, IL-17CT, IL-17CU, IL-17CV, IL-17CW, IL-17CX, IL-17CY, IL-17CZ, IL-17DA, IL-17DB, IL-17DC, IL-17DD, 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Non-type 2 inflammation (Innate)
 IL-1, IL-2, IL-6, IL-8, IL-9, IL-10, IL-12, IL-15, IL-16, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-28, IL-29, IL-30, IL-31, IL-32, IL-33, IL-34, IL-35, IL-36, IL-37, IL-38, IL-39, IL-40, IL-41, IL-42, IL-43, IL-44, IL-45, IL-46, IL-47, IL-48, IL-49, IL-50, IL-51, IL-52, IL-53, IL-54, IL-55, IL-56, IL-57, IL-58, IL-59, IL-60, IL-61, IL-62, IL-63, IL-64, IL-65, IL-66, IL-67, IL-68, IL-69, IL-70, IL-71, IL-72, IL-73, IL-74, IL-75, IL-76, IL-77, IL-78, IL-79, IL-80, IL-81, IL-82, IL-83, IL-84, IL-85, IL-86, IL-87, IL-88, IL-89, IL-90, IL-91, IL-92, IL-93, IL-94, IL-95, IL-96, IL-97, IL-98, IL-99, IL-100, IL-101, IL-102, IL-103, IL-104, IL-105, IL-106, IL-107, IL-108, IL-109, IL-110, IL-111, IL-112, IL-113, IL-114, IL-115, IL-116, IL-117, IL-118, IL-119, IL-120, IL-121, IL-122, IL-123, IL-124, IL-125, IL-126, IL-127, IL-128, IL-129, IL-130, IL-131, IL-132, IL-133, IL-134, IL-135, IL-136, IL-137, IL-138, IL-139, IL-140, IL-141, IL-142, IL-143, IL-144, IL-145, 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Legend:
 GM-CSF=granulocyte-macrophage colony-stimulating factor;
 Ig=immunoglobulin;
 IL=interleukin; IL2=innate lymphoid cell type 2; NKT=natural killer T cells;
 T_H17=Th17 helper type 17; T_H2=Th2 helper type 2 cell;
 TSLP=thymic stromal lymphoprotein.

From Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. *Chest*. 2014;145(1):96S-97S. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Broader Blockade of Type 2 Cytokines IL-4 and IL-13 Improves Outcomes

- Dupilumab
 - Targets IL-4 receptor alpha
 - Prevents IL-4 and IL-13 from binding to IL-13 receptor
- Works downstream via jak-stat dependent pathways to
 - Prevent IL-4 mediated production of IgE
 - Prevent IL-13 mediated eNO and mucus production
 - Prevent IL-4 and IL-13 mediated trafficking of eosinophils into the tissue

Dupilumab Anti IL-4/13

- Reduces Exacerbations
 - Improves Lung Function
 - Improves Quality of Life
 - Facilitate Corticosteroid Withdrawal
- Also approved for atopic dermatitis, chronic rhinosinusitis, eosinophilic esophagitis, prurigo nodularis

What about blocking epithelial alarmins?

Inflammatory mechanisms and pathobiologic features leading to severe asthma
Inflammatory mechanisms associated with granulocyte inflammation.

Type 2 inflammation (Antigen)
IL-4, IL-5, IL-13, IL-33, ILC2, Th2, Eosinophils, GM-CSF, IL-25, IL-35, IL-36, IL-37, IL-38, IL-39, IL-40, IL-41, IL-42, IL-43, IL-44, IL-45, IL-46, IL-47, IL-48, IL-49, IL-50, IL-51, IL-52, IL-53, IL-54, IL-55, IL-56, IL-57, IL-58, IL-59, IL-60, IL-61, IL-62, IL-63, IL-64, IL-65, IL-66, IL-67, IL-68, IL-69, IL-70, IL-71, IL-72, IL-73, IL-74, IL-75, IL-76, IL-77, IL-78, IL-79, IL-80, IL-81, IL-82, IL-83, IL-84, IL-85, IL-86, IL-87, IL-88, IL-89, IL-90, IL-91, IL-92, IL-93, IL-94, IL-95, IL-96, IL-97, IL-98, IL-99, IL-100.

Non-type 2 inflammation (Antigen, pollutants, microbes, and viruses)
IL-1, IL-2, IL-6, IL-8, IL-9, IL-10, IL-12, IL-17, IL-18, IL-20, IL-21, IL-22, IL-23, IL-24, IL-26, IL-27, IL-28, IL-29, IL-30, IL-31, IL-32, IL-34, IL-35, IL-36, IL-37, IL-38, IL-39, IL-40, IL-41, IL-42, IL-43, IL-44, IL-45, IL-46, IL-47, IL-48, IL-49, IL-50, IL-51, IL-52, IL-53, IL-54, IL-55, IL-56, IL-57, IL-58, IL-59, IL-60, IL-61, IL-62, IL-63, IL-64, IL-65, IL-66, IL-67, IL-68, IL-69, IL-70, IL-71, IL-72, IL-73, IL-74, IL-75, IL-76, IL-77, IL-78, IL-79, IL-80, IL-81, IL-82, IL-83, IL-84, IL-85, IL-86, IL-87, IL-88, IL-89, IL-90, IL-91, IL-92, IL-93, IL-94, IL-95, IL-96, IL-97, IL-98, IL-99, IL-100.

Legend:
GM-CSF=granulocyte-macrophage colony-stimulating factor; Ig=immunoglobulin; IL=interleukin; ILC2=innate lymphoid cell type 2; NK11c=natural killer T cells; Th1=Th1 helper cell 1; Th17=Th17 helper type 2 cell; TSLP=thymic stromal lymphopoietin.

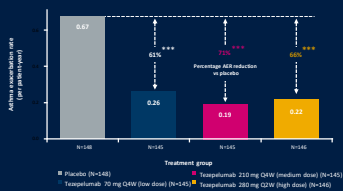
Pathobiologic features:
Hyperresponsiveness, remodeling, mucus production, and smooth-muscle constriction and hypertrophy.

Tezepelumab Targets TSLP and Blocks Inflammation from the Top of the Cascade

- Tezepelumab – human monoclonal antibody that binds to TSLP, specifically blocking it from interacting with its receptor
- Has potential to inhibit multiple downstream inflammatory pathways and enact broad effects on airway inflammation

Tezepelumab treatment reduced exacerbations vs placebo

Significant reduction in annualised AER for all tezepelumab treatment groups compared with placebo; P<0.001



Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. N Engl J Med. 2017;377(2):950-966.

An overview of biologic therapies used in inflammatory disorders

	Benralumab ^{1,2}	Reslizumab ³	Mepolizumab ⁴	Tezepelumab ⁵	Dupilumab ⁶	Cincalzumab ⁷
Mode of action	Humanized mAb to IL-6	Humanized mAb to IL-5	Humanized mAb to IL-5	Humanized mAb to TSLP	Humanized mAb to IL-4/IL-13	Humanized mAb to IL-1
Mode of action	Blocks IL-6 from interacting with its receptor, thereby reducing IL-6 signaling and downstream signaling	Blocks IL-5 from interacting with its receptor, thereby reducing IL-5 signaling and downstream signaling	Blocks IL-5 from interacting with its receptor, thereby reducing IL-5 signaling and downstream signaling	Targets and blocks TSLP from interacting with its receptor complex (TSLP/TL1R), suppressing inflammatory signaling	Blocks IL-4 and IL-13 signaling pathways	Blocks IL-1 signaling pathway
Administration	Subcutaneous	Intravenous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous
Indications	Add-on therapy for severe eosinophilic asthma (≥12 years of age) ¹	Add-on therapy for severe eosinophilic asthma (≥12 years of age) ³	Add-on therapy for severe eosinophilic asthma (≥12 years of age) ⁴	Not yet approved	Add-on therapy for severe eosinophilic asthma (≥12 years of age) ⁶ Severe atopic dermatitis (≥6 years of age) ⁶	Add-on therapy for severe allergic rhinitis (≥12 years of age) ⁷ Severe atopic dermatitis (≥6 years of age) ⁷
Approved dates	Asthma 2017 (USA), 2018 (EU)	Asthma 2016 (USA and EU)	Asthma 2015 (USA), 2016 (EU), 2017 (UK)	NA	Asthma 2019 (USA), 2019 (EU), 2019 (UK)	CRP 2016 (USA and EU), CRP 2016 (USA and EU)

1. Benralumab (Seroquel) 2017 (USA), 2018 (EU). 2. Benralumab (Seroquel) 2017 (USA), 2018 (EU). 3. Reslizumab (Cinryal) 2016 (USA and EU). 4. Mepolizumab (Nucala) 2015 (USA), 2016 (EU), 2017 (UK). 5. Tezepelumab (Tezspire) 2017 (USA), 2018 (EU), 2018 (UK). 6. Dupilumab (Dupixent) 2019 (USA), 2019 (EU), 2019 (UK). 7. Cincalzumab (Cincalza) 2016 (USA and EU), 2016 (USA and EU).

Summary

- Biologics are currently directed to TH2 pathways
- Biomarkers currently being studied most extensively are Th2 based in relation to current therapeutics

Summary

- Type 2 or T2 high asthma can be eosinophilic, allergic, or mixed
- Type 2 cytokines IL-4, IL-13, and IL-5 lead to airway remodeling, nitric oxide production, smooth muscle contractility, and eosinophil activation and recruitment
- Non type 2 or T2 low asthma can be neutrophilic or paucigranulocytic
- Neutrophilic asthma has poorer response to corticosteroids, higher associations with fixed airflow obstruction
- Paucigranulocytic asthma demonstrates uncoupling of airway structural changes and remodeling from inflammation
